An Emerging Era of Clinical Benefit From Gene Therapy

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EDITORIAL

An Emerging Era of Clinical Benefit From Gene Therapy

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The report in this issue of *JAMA* by Hacein-Bey Abina and colleagues[1] provides strong evidence that gene therapy using myeloid/lymphoid conditioning combined with subsequent infusion of lentivector-transduced autologous CD34$^+$ hematopoietic stem cells (HSCs) achieves substantial restoration of immune function associated with prolonged clinical benefit to patients with severe phenotype Wiskott-Aldrich syndrome (WAS). Prior to treatment, 6 of the 7 patients included in the study had the highest WAS severity disease score of 5; all patients had experienced serious clinical events and complications that are the hallmark of classic WAS, including recurrent viral or bacterial infections, bleeding due to microthrombocytopenia, severe eczema, vasculitis, enteropathy, and other autoimmune problems.

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It took 6 months or longer for the gene therapy to result in sufficient outgrowth of autologous gene-corrected T and B cells to begin to achieve the level of functional improvement of immunity needed to protect against or clear opportunistic infections and to begin to ameliorate autoimmune complications of WAS. The 1 patient who died at 7 months following gene therapy succumbed to preexisting severe opportunistic viral infection and severe autoinflammatory lung disease. However, the other 6 patients receiving the treatment had sustained improvements in quality of life. Among these patients, chronic infections resolved, eczema cleared, bleeding subsided, and severe autoimmune problems such as vasculitis substantially improved. At the time of the last follow-up (median follow-up time of 27 months after gene therapy), all 6 surviving patients reportedly showed sustained clinical benefit. The authors are cautious about claiming substantial correction of humoral immunity, but it is clear that measures of B-cell marking and function indicate progression toward achieving independence from immunoglobulin replacement. Although there was definite evidence of correction of microthrombocytosis and cessation of bleeding complications, the increase in platelet counts for the most part did not reach the normal range.

The impressive clinical response among these 6 patients reported by Hacein-Bey Abina and colleagues was achieved in the context of a long line of research by many groups of investigators striving toward the goal of clinically beneficial gene therapy. The earliest attempts involving gene therapy for adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID) targeting T lymphocytes in the early 1990s did not achieve sustained clinical benefit. The first unequivocal demonstration of substantial and durable clinical benefit from gene therapy mediated by profound restoration of T-cell immunity was achieved using murine retrovirus vector–transduced autologous CD34$^+$ HSCs to treat infants with X-linked SCID.[2,3] No conditioning regimen was used in those studies because selective outgrowth and persistence of T-cell gene marking was enough to achieve substantial durable clinical benefit even though there was no persistent gene marking correction of B cells or natural killer cells. Many of the authors of those pioneering studies[2,3] are also the authors of the current gene therapy trial for WAS.

In contrast to X-linked SCID, initial attempts to use a similar approach to gene therapy for ADA-SCID by infusion of autologous HSCs transduced with a murine retrovirus vector without prior myeloid conditioning did not result in the desired levels of gene marking or substantive clinical benefit. Aiuti and colleagues[4] showed that use of modest levels of busulfan myelosuppressive conditioning prior to the infusion of transduced gene-corrected autologous HSCs substantially enhanced the level of durable gene marking in multiple lineages and that this was the critical factor that achieved sustained clinical benefit from gene therapy in patients with ADA-SCID.

The early success of the 2 major trials of X-linked SCID gene therapy using a murine retrovirus vector was limited by the development of acute lymphocytic leukemia at 3 to 5 years following gene therapy in 5 of the 18 infants treated, who all had long-term gene marking and immune reconstitution.[5,6] Detailed studies of the pattern of vector insertion in the patients who developed leukemia and of other treated patients revealed a particular tendency of murine retrovirus vectors to insert into enhancer regions of the genome, including the 5′ and promoter regions of genes in general and certain proto-oncogenes in particular.[7] Vector insertional genotoxicity has been observed in some other gene therapy studies using murine retrovirus vectors.[8,9] However, no insertional genotoxicity events have been observed in any of the patients with ADA-SCID treated with murine retrovirus vector gene therapy.[4]

Of particular relevance to the current report by Hacein-Bey Abina et al[1] is an earlier gene therapy trial for WAS using a murine retrovirus vector with preparative conditioning, which resulted in immune reconstitution and substantial clinical benefit.[9] However, 7 of 9 treated patients eventually developed lymphoid or myeloid leukemia.[10] In a recent report of gene therapy treatment of 9 infants with X-linked SCID, a murine retrovirus vector was modified to remove strong enhancer/activator elements in the long terminal repeat.[11] This modification was referred to as self-inactivation (SIN) because the lesion introduced into the 3′ long terminal repeat is subsequently transferred to the 5′ long terminal repeat as a consequence of the events required for vector insertion into the target cell genome. An internal promoter must be incorporated into a SIN-modified vector because it lacks promoter activity from the virus long terminal repeat. The SIN modification resulted in substantially less outgrowth of clones of cells containing inserts in oncogenes, and no genotoxicity events were ob-

served in the infants with X-linked SCID treated with SIN murine retrovirus vector.[11]

In the last 16 years, a new class of integrating gene therapy viral vector has been developed by substantial modification of human immunodeficiency virus (HIV) type 1 that incorporates the SIN safety feature. Self-inactivation HIV lentivectors appear to have a substantially different, and likely safer, pattern of integration into the target cell genome.[12,13] Self-inactivation lentivector is less likely to target proto-oncogenes and does not particularly target insertion to the 5′ end of genes or to enhancer regions of the genome. In addition, any clones of cells in which the lentivector has inserted into a proto-oncogene appear less likely to expand uncontrolled in vivo. It took quite some time from the initial development of the SIN lentivector concept to its clinical use. Concern about the insertional genotoxicity potential of unmodified murine retrovirus vectors has driven the move away from murine retrovirus vectors to use of SIN lentivirus vectors. Furthermore, emerging evidence from use in clinical trials suggests that lentivirus vectors may more efficiently target transduction of long-term permanently repopulating HSCs. Thus, lentivectors appear to be not only safer but more effective than murine retrovirus vectors. Clinical benefit from gene therapy using lentivectors has been demonstrated for X-linked adrenoleukodystrophy, metachromatic leukodystrophy, and thalassemia.[14-16]

The report by Hacein-Bey Abina et al in this issue of *JAMA*[1] is not the first publication reporting clinical benefits following gene therapy for WAS using a lentivector. In 2013, Aiuti and colleagues[13] reported that they had infused lentivector-transduced autologous HSCs following conditioning to treat 3 children aged 1 to 3 years with WAS severity scores of 3 to 4. At 20 to 32 months' follow-up, there was substantial immune correction and clinical resolution of eczema and bleeding. The results presented by Hacein-Bey Abina and colleagues[1] substantially extend the findings reported by Aiuti and colleagues[13] by demonstrating correction and clinical benefit to a larger group of older patients entering the study with significantly greater severity and extent of WAS-related clinical problems.

Taken together, the available evidence demonstrates substantial sustained clinical benefit following gene therapy for certain diseases. Correction of immune deficiencies, thalassemia, and metabolic disorders with integrating vectors is only one area of success. Chimeric T-cell receptor gene therapy is successfully treating B-cell malignancies.[17] Gene therapy with adeno-associated virus vectors has been used to restore vision to patients with an inherited abnormality of the retina[18] and to correct a rare type of hemophilia.[19] Virus vectors are not likely to be the last word in gene therapy. New methods of precise gene targeting using zinc-finger nucleases, transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPRs) have just begun to emerge, and likely in the near future, these methods also will result in substantive clinical benefit for patients.[20] At a time when many are championing personalized medicine, no advance is as representative of that fundamental biological approach as gene therapy.

ARTICLE INFORMATION

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REFERENCES

1. Hacein-Bey Abina S, Gaspar HB, Blondeau J, et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. *JAMA*. doi:10.1001/jama.2015.3253.

2. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science*. 2000;288(5466):669-672.

3. Gaspar HB, Parsley KL, Howe S, et al. Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. *Lancet*. 2004;364(9452):2181-2187.

4. Aiuti A, Cattaneo F, Galimberti S, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med*. 2009;360(5):447-458.

5. Hacein-Bey-Abina S, Garrigue A, Wang GP, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. *J Clin Invest*. 2008;118(9):3132-3142.

6. Howe SJ, Mansour MR, Schwarzwaelder K, et al. Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. *J Clin Invest*. 2008;118(9):3143-3150.

7. Deichmann A, Brugman MH, Bartholomae CC, et al. Insertion sites in engrafted cells cluster within a limited repertoire of genomic areas after gammaretroviral vector gene therapy. *Mol Ther*. 2011;19(11):2031-2039.

8. Ott MG, Schmidt M, Schwarzwaelder K, et al. Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of *MDS1-EVI1*, *PRDM16* or *SETBP1*. *Nat Med*. 2006;12(4):401-409.

9. Boztug K, Schmidt M, Schwarzer A, et al. Stem-cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med*. 2010;363(20):1918-1927.

10. Braun CJ, Boztug K, Paruzynski A, et al. Gene therapy for Wiskott-Aldrich syndrome—long-term efficacy and genotoxicity. *Sci Transl Med*. 2014;6(227):227ra33.

11. Hacein-Bey-Abina S, Pai SY, Gaspar HB, et al. A modified γ-retrovirus vector for X-linked severe combined immunodeficiency. *N Engl J Med*. 2014;371(15):1407-1417.

12. Biffi A, Bartolomae CC, Cesana D, et al. Lentiviral vector common integration sites in preclinical models and a clinical trial reflect a benign integration bias and not oncogenic selection. *Blood*. 2011;117(20):5332-5339.

13. Aiuti A, Biasco L, Scaramuzza S, et al. Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. *Science*. 2013;341(6148):1233151.

14. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science*. 2009;326(5954):818-823.

15. Biffi A, Montini E, Lorioli L, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. *Science*. 2013;341(6148):1233158.

16. Cavazzana-Calvo M, Payen E, Negre O, et al. Transfusion independence and *HMGA2* activation after gene therapy of human β-thalassaemia. *Nature*. 2010;467(7313):318-322.

17. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371(16):1507-1517.

18. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008;358(21):2240-2248.

19. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014;371(21):1994-2004.

20. Tebas P, Stein D, Tang WW, et al. Gene editing of *CCR5* in autologous CD4 T cells of persons infected with HIV. *N Engl J Med*. 2014;370(10):901-910.